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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,905	PARIS ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15, 21-24, 31,62-79* is/are pending in the application.

4a) Of the above claim(s) *77 and 78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,21-24,31,62-71,73,74-76 and 79* is/are rejected.

7)☒ Claim(s) *72* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/01/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/1/2009 has been entered.

Status of the claims

2. Claims 15, 21-24, 31, 62-73 were pending in the application. Claims 15, 21-24, 31, 63, 71-72 were amended by applicant. Claims 74-79 are new.

Applicant originally elected L-685,458 which was searched and found free of the prior art. The search was expanded and the species DAPT was found.

Newly submitted claims 77-78 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 77-78 are drawn to DAPM and JLK-6, respectively, which are not corresponding to elected or examined species. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 77 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 15, 21-24, 31, 62-76 and 79 are presented for examination on the merits. Claims 77-78 are withdrawn as not drawn to the elected species.

Applicant's arguments, see pages 7-9, filed 12/1/2009, with respect to the rejection(s) of claim(s) 15, 21-24, 31, 62-73 under 112 1st written description have been fully considered and are deemed persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the 112 1st scope of enablement rejection set forth below.

Applicant's arguments with respect to claims 15, 21-24, 31, 62-73 as unpatentable over Weng et al. in view of Jundt et al. have been considered but are moot in view of the new ground(s) of rejection as set forth below.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 15, 62-70, 73 and 79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for L-685,458 and DAPT (and also DAPM and JLK-6) and analogs thereof in treating human brain endothelial cells, human glioblastoma U-87 MBG and human lung adenocarcinoma A-549, does not reasonably provide enablement for any gamma-secretase with no common structure to L-685,458, DAPT, (or DAPM and JLK-6) or for treating any tumor in general, including malignant breast, colon, kidney, bladder, and/or head /neck tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to use the invention commensurate in scope with these claims. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the invention. The claims are drawn to methods reducing solid tumor volume in an animal or human in need thereof comprising inhibiting gamma-secretase activity and angiogenesis in said tumor, independent of Notch cleavage, to reduce solid tumor volume in said animal or human.

State of the prior art. At the time the invention was made, the need for new agents with novel mechanisms of action to prevent cancer was perhaps the most urgent need in the entire field of chemoprevention. The continuing magnitude of the cancer problem, and the failure of conventional chemotherapy of advanced invasive disease to effect major reductions in the mortality rates for the common forms of epithelial malignancy such as carcinoma of the lung, colon, breast, prostate and pancreas, indicate that new approaches to the control of cancer were critically needed (Sporn et al. Carcinogenesis, 2000). Evaluation of anticancer agents depends critically on the interaction of basic, pre-clinical and clinical research in a structure network (Zips et al. In vivo 2005, e.g., Figure 1). Experimental evaluation of new anticancer agents is realized by means of in vitro and in vivo methods to describe whether or not a new drug is effective against cancer cells. The so-called functional assays basically measure survival of tumor cells with and without therapy, e.g., as a total number of cells, a number of colonies, tumor volume or tumor cure rate. Non-functional assays are often also refereed to as mechanistic investigations, e.g., assessment of drug effects on apoptotic pathways or intracellular signaling and are important mechanism of

action. Both functional and non-functional assays are essential for the evaluation of anticancer agents.

However, not all tumor cell lines show the same magnitude of response to anticancer agents. For most anticancer agents the underlying reasons for intertumoral heterogeneity are poorly understood. Experimental data suggest that expression levels of the molecular target and specific genetic alterations are important determinant for response. For example, the response to inhibitors of epidermal growth factor receptor (EGFR) shows a considerable heterogeneity between different cell lines in vitro and in vivo (Zips et al. page 2). Expression patterns of EGFR and HER2/neu are distinct between different tumor cell lines and seem to correlate with response to the corresponding inhibitor. In line with experimental studies, clinical data show that specific mutations correlate with the individual response of tumors to EGFR inhibition. Experience with EGFR inhibitors clearly shows the importance of evaluating new anticancer drugs in a range of different tumor cell lines. The use of “outliner” or “best-responding” cell lines may help in studying the mechanism of action of a particular drug, but may also lead to an overestimation of its therapeutic potential. Systematic exploration of heterogeneity by molecular profiling will help to tailor new approaches and to identify patients who might benefit from new anticancer agents.

Breadth of the claims. The claims are extremely broad, encompassing reduction of any solid tumor at any stage of development of any type of cancer in any animal by administration of any gamma-secretase.

Working examples. The working examples are limited to: Example 1: drawn to the effects of L-685,485, DAPM, DAPT, JLK-6 on the proliferation and differentiation of primary cultures of human brain endothelial cells (see [0065]-[00076] of the corresponding PGPUB application US 2004/0229816) showed that the gamma-secretase inhibitors, all dose dependently inhibited the proliferation of human brain endothelial cells without inducing cellular toxicity. Example 2: drawn to the effect of the gamma-secretase inhibitors on the sprouting of microvessels from explants of rat aortae (see [0077]-[0080]) showed that the gamma-secretase inhibitor DAPT appeared to stimulate the sprouting of microvessels at 5 uM and to inhibit the sprouting of microvessels at 20 uM. Additionally the gamma-secretase inhibitor L-685,458 inhibited the sprouting at 1 and 5 uM further supporting the involvement of a gamma-secreatase-like activity during angiogenesis. Example 3: drawn to the effects of DAPT on the human glioblastoma U-87 MG tumor cells, xenografted under the skin of nude mice ([0081]-[0084]) showed that the gamma secretase inhibitor DAPT inhibited the growth of U-87 MG brain tumors but also reduced the volume of the tumors by More than 90% after one week of treatment. A decreased vascularization of the tumors was evaluated and observed in U-87 MG tumors treated with DAPT suggesting ability to inhibit tumor angiogenesis in vivo. The effect of DAPT on the growth of the human lung adenocarcinoma cell line A-549 revealed that it potently suppressed the growth of A-549 lung adenocarcinoma in nude mice. Vascularization of A-549 tumors xenotransplanted into mice was reduced by DAPT and JLK-6.

Guidance in the specification. The specification provides little guidance regarding practice of the claimed methods with regards to other cells lines, or even other gamma-secretases beyond DAPT in relation to tumor shrinkage.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). In the instant application, Applicants have extrapolated treating any solid tumor with any gamma-protease, but as stated by Zips et al.: "not all tumor cell lines show the same magnitude of response to anticancer agents. For most anticancer agents the underlying reasons for intertumoral heterogeneity are poorly understood". Moreover, the heterogeneity of inhibitors' responses, as evidenced by the instant specification and also taught by Zips et al. clearly shows the importance of evaluating new anticancer drugs in a range of different tumor cell lines. The use of "outliner" or "best-responding" cell lines may help in studying the mechanism of action of a particular drug, but may also lead to an overestimation of its therapeutic potential. Systematic exploration of heterogeneity by molecular profiling will help to tailor new approaches and to identify patients who might benefit from new anticancer agents.

Amount of experimentation necessary. It would require extensive research to determine whether the response of the whole genus of gamma-secretases to reduction of any kind of solid tumor in vivo. Applicants have identified a useful method, but essentially all of the work required to ultimately develop a treatment method encompassing any solid tumors of any stage of development with any gamma-secretase inhibitors beyond those illustrated in the Examples has been left for others, based on the state of the art, as set forth

above by Sporn et al. and Zips et al., the working examples and disclosure of the instant application also described above.

For the reasons discussed, it would require undue experimentation for one skilled in the art to use the claimed methods.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 15, 73 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jundt et al. (Blood, November 16, 2002)

Jundt et al. disclose a method of reducing solid tumor volume in an animal or human in need thereof, comprising administering a gamma-secretase inhibitor

(DAPT). In this study, Jundt et al. established a xenotransplant model in SCID mice, where Jundt et al. injected the Hodgkin cell line KM-H2 subcutaneously. KM-H2 cells were not tumorigenic in SCID mice (0/8 mice) within three months. However, irradiated Jagged1-expressing cells dramatically increased tumor cell growth of KM-H2 cells (8/11 mice). Jundt et al. tested the functional gamma-secretase inhibitor DAPT activity in proliferation assays in which tumor cells of Hodgkin (L1236, HD LM2) and anaplastic large cell lymphoma (Karpas 299- SU-DHLI) were activated by their cognate ligand Jagged1. As expected, stimulation of tumor cells resulted in an exponential increase in growth rates. This increase could efficiently be blocked by DAPT in a dose-dependent manner indicating that this novel gamma-secretase inhibitor can control tumor cell growth in vitro.

Jundt et al. go on to teach that at the time of writing their report they were investigating whether DAPT potently inhibited tumor cell growth in vivo.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use DAPT for in vivo studies of control of tumor cell growth Hogkin and anaplastic large cell lymphoma as taught also by Jundt et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so since DAPT showed the ability to control tumor cell growth in vitro and in vivo as taught by Jundt et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in reducing tumor volume in an animal or human since Jundt et al. since the in vitro results expressed efficient blocking of the tumor growth rates using DAPT in a dose-dependent manner and efficiently controlling tumor cell growth

(see Abstract, page 158a) thus reducing solid tumor volume. With regards to the limitations "inhibiting angiogenesis" and "independent of Notch cleavage", please note that these limitations necessarily read upon administration of DAPT to a Hodgkin or anaplastic large cell tumor since the active steps for in vivo treatment (i.e., administering to animal or human) would be identical to those instantly claimed. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. (See MPEP 2112 and 2141.02).

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. Claims 15, 21-24, 31, 71, 74-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jundt et al. (Blood, November 16, 2002) in view of Dovey et al. (J Neurochem, 2001).

Jundt et al. disclose a method of reducing solid tumor volume in an animal or human in need thereof, comprising administering a gamma-secretase inhibitor (DAPT). In this study, Jundt et al. established a xenotransplant model in SCID

mice, where Jundt et al. injected the Hodgkin cell line KM-H2 subcutaneously. KM-H2 cells were not tumorigenic in SCID mice (0/8 mice) within three months. However, irradiated Jagged1-expressing cells dramatically increased tumor cell growth of KM-H2 cells (8/11 mice). Jundt et al. tested the functional gamma-secretase inhibitor DAPT activity in proliferation assays in which tumor cells of Hodgkin (L1236, HD LM2) and anaplastic large cell lymphoma (Karpas 299- SU-DHLI) were activated by their cognate ligand Jagged1. As expected, stimulation of tumor cells resulted in an exponential increase in growth rates. This increase could efficiently be blocked by DAPT in a dose-dependent manner indicating that this novel gamma-secretase inhibitor can control tumor cell growth in vitro.

Jundt et al. go on to teach that at the time of writing their report they were investigating whether DAPT potently inhibited tumor cell growth in vivo.

Jundt et al. do not expressly teach a specific type of administration when applying DAPT in vivo.

Dovey et al. discloses administration of DAPT in vivo to transgenic mice which were dosed orally with DAPT at a volume of 100 mg/kg with compound formulated in corn oil, 5% v/v ethanol or vehicle alone (see pages 175-176) s.c. (subcutaneously). See also page 177.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer DAPT to treat tumors as taught by Jundt et al. using, e.g., subcutaneous administration which was used in vivo studies using DAPT as taught by Dovey et al. One of ordinary skill in the art at the time the invention was made would have been motivated to determine all the possible

forms of administration of DAPT including orally and/or topically. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since such adjustments to the type of administration were known to be well within the purview of those of ordinary skill in the art since the art recognizes that standard modes of administration for pharmaceutical compositions.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Objection

8. Claim 72 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

9. No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose

telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MMCG 01/2010

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654